Appendix 1: Grade evidence profiles and narrative summary tables (as supplied by the authors)

Table 1: GRADE evidence profile for intent-to-start early versus intent-to-defer

	Quality assessment					No. of patients		Effect			
No. of studies and design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early start dialysis	Late start dialysis	Relative HR (95% CI)	Absolute	Quality	Importance
Mortality											
Randomized trials: follow-up mean 3.59 y; assessed with all -cause mortality											
1[1]	No serious RoB	No serious inconsistency	No serious indirectness	Serious*	None	152/404 (37.6%)	155/424 (36.6%)†	1.04 (0.83–1.3)	11 more per 1000 (range –51 to 81)	⊕⊕⊕O Moderate	Critical
Observational studies: follow-up 1-11 y; assessed with all-cause mortality											
15[2]	Very serious‡	Very serious§	No serious indirectness	No serious imprecision	None	—	36.6%†	1.04 (1.03–1.05)‖	11 more per 1000 (range 9–14)	⊕OOO Very low	Critical
Quality of life											
Randomized trials: follow-up mean 6 m; measured with SF-36 at 0.5, 1, 2, and 3 y; better indicated by lower values											
1[3]	No serious RoB	No serious inconsistency	No serious indirectness	No serious imprecision	None	307	335	—	MD 1 higher (no CI provided)	⊕⊕⊕⊕ High	Critical
Observational studies (follow-up 1 years; measured with: SF-36; better indicated by lower values)											
1[4]	Serious¶	No serious inconsistency	Serious**	No serious imprecision††	None	147	90	—	MD 2.5 higher (no CI provided)	⊕OOO Very low	Critical
Hospitalizations											
Randomized trials: follow-up median 4.15 y; measured with hospitalization (days); (early–late); better indicated by lower values											
1[3]	No RoB	No serious inconsistency	No serious indirectness	Serious‡‡	None	307	335	—	MD 8 higher (range –2 to 17)	⊕⊕⊕O Moderate	Important
Observational studies: follow-up 1-6 y; measured with number of hospitalizations; better indicated by lower values											
5[5–9]	Serious§§	Serious□□	Serious¶¶	No serious imprecision	None	—	—	—	See narrative summary (Appendix 3)	⊕OOO Very low	Important
Nutritional status											
Observational studies: follow-up mean 6 months; measured with total body nitrogen (% predicted based on population norms); better indicated by higher values											
1[10]	Very serious***	No serious inconsistency	Serious†††	No serious imprecision	None	26	108	—	MD 18 higher (range 6–30)	⊕OOO Very low	Not important

Note: HR=hazard ratio; MD=mean difference; RoB= risk of bias; SF-36=36-item Short Form health survey.
*Optimal information size criterion met for control event rate = 40% and relative risk reduction (RRR) 25%; 95% CI crosses 25% decision threshold (HR 1.30); therefore, rated down for imprecision.
†Based on control group event rate (36.6%) in IDEAL trial.

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‡Multivariable models did not include information pertaining to indication for starting dialysis (e.g., symptoms of uremia or hypervolemia); therefore, indication bias was likely present and not completely adjusted for in most observational studies.
§An I^2 of 97% indicates severe heterogeneity that was not explained in subgroup analyses that included studies with: adjustment for nutritional markers, hemodialysis patients only, peritoneal dialysis patients only, calculated glomerular filtration rate (GFR), and estimated GFR.
‖Hazard ratio is per 1 mL/min/1.73 m^2 GFR increment.
¶Baseline prognostic variables unbalanced, but not statistically significant; however, unmeasured factors contributing to indication bias likely present.
**Early and late cohorts defined as GFR 7.1 ±2.5 and 4.9 ±1.7 mL/min by averaging timed urea and creatinine clearance; both groups would be considered late start compared with recent studies, including the IDEAL trial.
††Kidney Disease Quality of Life Physical and Mental Component summaries did not differ between groups; statistical comparisons only provided for individual components that were significant. Study adequately powered to detect minimal important difference of 3 points assuming SD 12, alpha 0.05, and power 0.8.
‡‡Study may have been underpowered to detect clinically meaningful differences in hospitalization; unable to obtain normalized hospitalization data from authors.
§§2 of 5 studies[5,7] had serious risk of indication bias.
‖‖Although different reported measures of effect and clinical heterogeneity precluded pooling, effect estimates ranged between beneficial and harmful association with later initiation of dialysis.
¶¶Early vs. late cohorts defined variably across 3 studies: elective starter vs. initial refuser, [6] GFR as greater or less than 5 mL/min,[7] and highest vs. lowest quartile of serum albumin and creatinine.[5]
***Large differences in age, gender, diabetes, presence of heart disease, and late referral (< 3 months, 32% vs. 11% in late vs. early start groups, respectively) were not adjusted for in main analysis; major differences in patient characteristics may have accounted for the difference in body nitrogen in this study.
†††Surrogate marker; not validated for predicting mortality or nutritional status.

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Table 2. GRADE evidence profile for resource use of only randomized trials

No. of studies and design	Quality assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients: Intent for early start dialysis	Intent for late start dialysis	Effect: Relative (95% CI)	Absolute (MD = early–late)	Quality	Importance
Dialysis											
Months: follow-up mean 4.15 y; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	No serious indirectness	No serious imprecision	None	307	335	–	MD 3.8 higher (range 0.3–7.3)	⊕⊕⊕⊕ High	Important
Costs (follow-up mean 4.15 y; measured with CA$; better indicated by lower values											
1†	No serious RoB	No serious inconsistency	No serious indirectness	No serious imprecision	None	307	335	–	MD 10 777 higher (range 313–22 801)†‡	⊕⊕⊕⊕ High	Important
Hospitalization											
Days: follow-up mean 4.15 y; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	No serious indirectness§	Serious‖	None	307	335	–	MD 8 higher (range –2 to 17)	⊕⊕⊕O Moderate	Important
Costs: follow-up mean 4.15 y; measured with A$; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	Serious	Serious‖	None	307	335	–	MD 5112 higher (range –3662 to 13 247)	⊕⊕⊕O Low	Important
Transportation											
Costs: follow-up mean 4.15 y; measured with A$; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	Serious¶	No serious imprecision**	None	307	335	–	MD 3610 higher (range 1111–9959 higher)**	⊕⊕⊕O Moderate	Important
Outpatient											
Visits nonadmitted: follow-up mean 4.15 y; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	No serious indirectness	Serious‖	None	307	335	–	MD 0 higher (range –3 to 3)	⊕⊕⊕O Moderate	Important
Costs nonadmitted: follow-up mean 4.15 months; measured with A$ better indicated by lower values											
1*	No serious RoB	No serious inconsistency	Serious††	Serious‖‡‡	None	307	335	–	MD 129 lower (range –1155 to 1070)	⊕⊕OO Low	Important
Visits GP/HP: follow-up mean 4.15 years; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	No serious indirectness	Serious‖	None	307	335	–	MD 0 higher (range –6 to 5)	⊕⊕⊕O Moderate	Important
Costs GP/HP: follow-up mean 4.15 y; measured with A$; better indicated by lower values											
1*	No serious RoB	No serious inconsistency	Serious††	Serious‖	None	307	335	–	MD 259 lower (range –722 to 242)	⊕⊕OO Low	Important

Note: A$=Australian dollars; CA$=Canadian dollars; GP=general practitioner; HP=allied health care practitioner; MD=mean difference; Rob=risk of bias.

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*Harris et al.[3]
†Canadian dialysis costs used microcosting data from Lee[11] inflated to 2008 CA$. Cost of $10 440 (2008 CA$) if a blend of 50% PD and 50% HD as per Harris et al.;[3] cost of $12 219 (2008 CA$) if a blend of 25% PD and 75% HD as per current Canadian estimates. Both scenarios assume 3.8 months of dialysis difference between groups.
‡Results were similar when Ontario costs[12] were used.
§Although hospitalization rates were derived from an Australian population,[3] it is unlikely that this effect varies significantly in a Canadian population; therefore, we did not rate down for indirectness.
‖Attrition may have decreased precision of estimate. Only 78% of IDEAL trial participants were in the economic study; however, stated reason was primarily because of delay in ethics approval. Not sure of power issues to detect differences for these outcomes. Confidence interval ranges between trivial and significant incremental costs that would lead to different decisions regarding strength of recommendation; hence, serious imprecision exists.
¶Australian setting; may differ from Canadian setting because of mix of home dialysis, especially peritoneal dialysis.[13]
**Travel costs estimated using distance travelled with application of unit costs for mode of transportation used.
††Reported in 2008 A$.
‡‡CI ranges between significant cost savings and greater incremental costs.

Table 3: Summary of studies assessing effect on mortality – not included in review by Susantitaphong et al.[2]

Study	Year	Quality assessment	Outcome measures	Notes
Fink[14]	1999	Serious RoB		Need additional data; GFR not presented; number lost to follow up not detailed
Kim[8]	2009	Serious to very serious RoB	No difference in crude survival between early and late starters (p=0.096), as defined as greater and less than 5 mL/min/1.73 m^2. No difference in survival curves between early and late starters (p=0.27)	Unadjusted analysis; no information on patients excluded
Rosansky[15]	2009	Difficult to assess	Patients aged 65–74 years with an eGFR of 5–9.9 at the initiation of dialysis have a 25% first year mortality rate; similarly aged patients with an eGFR of > 15 at initiation of dialysis have a 41.5% first year mortality rate	No information on characteristics of patients; no information on those lost to follow-up
Sjolander[16]	2011	Serious RoB	From initiation* method: HR 0.81 (95% CI 0.51–1.21) and HR 0.77 (95% CI 0.48–1.25) for intermediate and late (vs. early) From threshold† method: HR 0.62 (95% CI 0.39–0.98) and HR 0.56 (95% CI 0.35–0.91) for intermediate and late (vs. early) Inverse probability weighting method: equal trend for early and intermediate starters; better survival for late starters	Re-analysis of the study done by Evans et al.;[17] inverse probability weighting was used as a method to correct for lead-time and immortal time bias; many patient exclusions due to lack of repeated measures
Collins[18]	2011	Little RoB	HR with early initiation 0.97 (95% CI 0.66–1.41)	Subgroup analysis of IDEAL study[1]

Note: eGFR=estimated glomerular filtration rate; HR=hazard risk; RoB=risk of bias.
*From threshold examines from the time renal function dropped below a fixed threshold.
†From initiation refers to the baseline at which dialysis is initiated.

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Table 4: Summary of studies assessing effect on quality of life

Study	Year	Quality assessment	Outcome measures	Notes
Korevaar[4]	2002	Little RoB	Compared with patients who started dialysis later, patients who started earlier had significantly higher HR QOL for a number of dimensions immediately after start of treatment; after 12 mo, these differences disappeared	No confidence intervals presented
Harris[3]	2011	Little RoB	No significant difference in QOL between early and late starters (no further details for SF-36)	~50% of the patients did not complete 4-year follow-up

Note: HR=hazard risk; QOL=quality of life; RoB=risk of bias; SF-36=36-item Short Form health survey.

Table 5: Summary of studies assessing effect on hospitalization

Study	Year	Quality assessment	Outcome measures	Notes
Pupim[5]	2003	Serious RoB	9.61 (SD 15.46) days vs. 8.78 (SD 9.84) for lowest vs. highest quartile for number of days in hospital; unadjusted.	Lack of detail on lost to follow-up by group; only 50% of total sample reported 24-h creatinine clearance; lowest and highest quartile not defined
Tang[6]	2007	Serious RoB	2.13 (SD 1.13) episodes/person-year vs. 3.14 (SD 1.17) for elective starters vs. initial refusers (p=0.05); unadjusted analysis	Elective starters defined as people who chose to start dialysis early compared with those who refused. Baseline differences of eGFR between groups is negligible; SDs overlap
Shiao[7]	2008	Serious RoB	Late start of dialysis was associated with reduced risk for all-cause hospitalization (log rank, p = 0.025); adjusted analysis	Potential selection bias because initial dropouts not detailed by group; early vs. late start defined as greater and less than 5 mL/min/1.73 m^2, respectively
Kim[8]	2009	Serious to very serious RoB	1.6 (SD 2.2) days vs. 1.8 (SD 1.8) days for late vs. early starters (p=0.34); unadjusted analysis	Early and late start defined as greater or less than 5 mL/min/1.73 m^2, respectively
Coronel[9]	2009	Serious RoB	1.3 (SD 1.0) days for early start compared to 1.5 (SD 1.2) days in late start, not significant; 23.1 (SD 29) days compared to 20 (SD 22) days/patient/year, not significant	
Harris[3]	2011	Little RoB	48 (SD 64) days vs. 40 (SD 54) for early vs. late start group	Substudy of IDEAL trial; not all participants enrolled because of delay in obtaining ethics approval

Note: RoB=risk of bias.

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Table 6: Summary of studies assessing effect on nutritional status as measured by body nitrogen index

Study	Year	Quality assessment	Outcome measures	Notes
Cooper[10]	2003	Serious RoB	Nitrogen index was 106% (SD 9%) vs. 88% (SD 13%) in early vs. late starters, respectively	Technically a case-control study, although authors report it as a retrospective cohort; only baseline data presented with no follow-up

Note: RoB=risk of bias.

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